PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

IRINOTECAN 40 mg/2 ml FKSA

IRINOTECAN 100 mg/5 ml FKSA

IRINOTECAN 300 mg/15 ml FKSA

IRINOTECAN 500 mg/25 ml FKSA

Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 20 mg irinotecan hydrochloride trihydrate.

IRINOTECAN 40 mg/2 ml FKSA: One vial of 2 mL contains 40 mg of irinotecan hydrochloride trihydrate (40 mg/2 ml)

IRINOTECAN 100 mg/5 ml FKSA: One vial of 5 mL contains 100 mg of irinotecan hydrochloride trihydrate (100 mg/5 ml)

IRINOTECAN 300 mg/15 ml FKSA: One vial of 15 mL contains 300 mg of irinotecan hydrochloride trihydrate (3000 mg/15 ml)

IRINOTECAN 500 mg/25 ml FKSA: One vial of 25 mL contains 500 mg of irinotecan hydrochloride trihydrate (500 mg/25 ml)

Contains a sugar alcohol: sorbitol 45 mg/ml

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Yellow coloured solution free from visible particles.

pH is between 3,3 and 3,5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

IRINOTECAN FKSA is indicated for the treatment of patients with advanced colorectal cancer with a WHO performance status of 2 or lower:

- In combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease.
- As a single medicine in patients who have failed an established 5-fluorouracil containing treatment regimen.

4.2 Posology and method of administration

Posology

IRINOTECAN FKSA solution for infusion should be infused into a peripheral or central vein.

Recommended dosage in monotherapy (for previously treated patients):

350 mg/m^2 administered as an intravenous infusion over a 30- to 90-minute period every three weeks. (see sections 4.4 and 6.6)

Recommended dosage in combination therapy (for previously untreated patients): Safety and efficacy of **IRINOTECAN FKSA** in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with either of the following schedules (see section 5.1)

IRINOTECAN FKSA plus 5FU/FA in weekly schedule:

80 mg/m^2 administered as a weekly intravenous infusion over a 30- to 90-minute period followed by infusion with folinic acid and then by 5-fluorouracil over 6 weeks. This treatment is followed by a week rest.
The full dosage regimen is 80 mg/m^2 as a 30- to 90-minute infusion on Day 1 and then weekly for 6 weeks. Folinic acid 500 mg/m^2 IV as a 2-hour infusion, followed by 5-fluorouracil 2 000 mg/m^2 IV as 24-hour infusion, Day 1 and then weekly for 6 weeks. The treatment is to be repeated every 7 weeks.

IRINOTECAN FKSA plus 5FU/FA in every 2 weeks schedule:

180 mg/m^2 administered once every 2 weeks as an intravenous infusion over a 30- to 90 minute period, followed by infusion with folinic acid and 5-fluorouracil. The full dosage regimen is 180 mg/m^2 IV as a 30- to 90-minute infusion on Day 1 only. Folinic acid 200 mg/m^2 IV as a 2-hour infusion, followed by 5-fluorouracil 400 mg/m^2 IV bolus, followed by 5-fluorouracil 600 mg/m2 IV as a 22-hour infusion. The folinic acid and 5-

fluorouracil are repeated for two consecutive days. Repeat the cycle every two weeks.

Dosage adjustments

Delayed dosing: **IRINOTECAN FKSA** should not be administered until the neutrophil count remains above 1 500 cells/mm^3. In patients who experienced severe neutropenia or severe gastrointestinal adverse events such as diarrhoea, nausea and vomiting, dosing of **IRINOTECAN FKSA** should be delayed until there has been a full recovery of these effects, especially diarrhoea.

IRINOTECAN FKSA should be administered after appropriate recovery of all adverse events to grade 0 or 1 NCI-CTC grading (National Cancer Institute Common Toxicity Criteria) and when treatment-related diarrhoea is fully resolved. This must be strictly adhered to. At the start of a subsequent infusion of therapy, the dose of **IRINOTECAN FKSA and 5FU** when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events, a dose reduction of 15 to 20 % should be applied for **IRINOTECAN FKSA and/or 5FU** when applicable:

- Haematological toxicity (neutropenia grade 4, febrile neutropenia (neutropenia grade 3-4 and fever grade 2-4), thrombocytopenia and leukopenia (grade 4))
- Non-haematological toxicity (grade 3-4).

Treatment duration: Treatment with **IRINOTECAN FKSA** should be continued until there is an objective progression of the disease or an unacceptable toxicity.

Special populations

Patients with impaired hepatic function:

- Patients with a bilirubin >1,5 times the ULN should not be treated with **IRINOTECAN FKSA.** In patients with a bilirubin ≤1,5 times the upper limit of the normal range (ULN), a dose of 350 mg/m^2 **IRINOTECAN FKSA** is recommended.
- In patients with bilirubin >1 and ≤1,5 times the upper limit of the normal range (ULN), the risk of severe neutropenia is increased.

  Thus, frequent monitoring of complete blood counts should be conducted in this patient population.

Patients with impaired renal function:

No specific pharmacokinetic studies have been performed in patients with renal impairment. (see sections 4.4 and 5.2).

Elderly:

No specific pharmacokinetic studies have been performed in the elderly. However, the dose should be chosen carefully in this population due to their greater frequency of decreased hepatic, renal or cardiac function. This population should require more intense surveillance (see section 4.4).

Paediatric population

The safety and efficacy of **IRINOTECAN FKSA** in children below 18 years of age have not yet been established.

No data is available

Method of administration

Intravenous administration.

Precautions to be taken before handling or administering the medicine.

For instructions on dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

- Patients with a history of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of **IRINOTECAN FKSA**. (see section 6.1)
- Chronic inflammatory bowel disease, and/or bowel obstruction or ileus. Patients should not be treated with **IRINOTECAN FKSA** until resolution of the ileus. (see section 4.4)
- Severe bone marrow failure, pre-existing or treatment-related.
- WHO performance status > 2.
- Pregnancy and breastfeeding (see section 4.4 and 4.6).

  Women of childbearing age receiving **IRINOTECAN FKSA** should be advised to avoid becoming pregnant and to inform the treating medical practitioner immediately should this occur (see section 4.6).
- Bilirubin >1,5 times the upper limit of the normal range.
- Children: The safety and efficacy of **IRINOTECAN FKSA** in children below 18 years of age have not been established.
- Concomitant use of the following: St John's Wort, ketoconazole, yellow fever vaccine. (see section 4.5)
- Live attenuated vaccine (see section 4.5)

4.4 Special warnings and precautions for use

IRINOTECAN FKSA should be used in patients with a good performance status of less than 2.

The use of **IRINOTECAN FKSA** should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a qualified oncologist.

It is strongly recommended that **IRINOTECAN FKSA** be administered only in healthcare institutions with adequately equipped facilities, including an intensive care unit.

Premedication with anti-emetic medicines are recommended in order to reduce nausea and vomiting associated with **IRINOTECAN FKSA** treatment. This treatment should be started at least 30 minutes before the infusion. In all instances where the use of **IRINOTECAN FKSA** is considered for chemotherapy, it is especially important to ensure that the patient understands the need for sufficiently prolonged antidiarrhoeal treatment and abundant fluid intake. In rare cases where it is predictable that the patient would comply poorly with the guidances for the management of side effects, a strict follow-up of the patient by the treating medical practitioner or hospitalisation is recommended.

Given the nature and frequency of adverse events, the expected benefit must be balanced in case of risk factors, especially WHO performance status = 2 (or Karnofsky Index <50).

When **IRINOTECAN FKSA** is used in monotherapy, it is usually prescribed with the every-3-weekdosage schedule. However, the weekly-dosage schedule (see section 5) may be considered in patients who may need a closer follow-up or who are at particular risk of severe neutropenia.

Delayed diarrhoea:

Apart from the diarrhoea shortly after the infusion of **IRINOTECAN FKSA,** patients should be aware of the high risk of delayed diarrhoea occurring more than 24 hours after the administration of **IRINOTECAN FKSA** and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on Day 5 after the infusion of **IRINOTECAN FKSA.** Patients should quickly inform their medical practitioner of its occurrence and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy, those with baseline hyperleukocytosis and those with performance status ≥ 2. If not properly treated,

diarrhoea can be life-threatening, especially if the patient is concomitantly neutropenic.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where **IRINOTECAN FKSA** has been administered. After discharge from the hospital the patients should obtain the prescribed medicines so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their medical practitioner or the department administering **IRINOTECAN FKSA** that diarrhoea is occurring.

The currently recommended antidiarrhoeal treatment is loperamide 4 mg for the first intake and then 2 mg every 2 hours. This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no case should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the antidiarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm^3).

In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea in the following cases:

- Diarrhoea associated with fever.
- Severe diarrhoea (requiring intravenous hydration).
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles.

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles (see section 4.2).

Haematology

In clinical studies, the frequency of NCI CTC Grade 3 and 4 neutropenia has been significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation. Patients with baseline serum total bilirubin levels of 1,0 mg/dL or more have also had a significantly greater likelihood of experiencing first-cycle Grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1,0 mg/dL.

Weekly monitoring of complete blood cell counts should be performed during **IRINOTECAN FKSA** treatment. Patients should be aware of the risk of infection and the significance of a fever. Febrile

neutropenia (temperature ≥ 38 °C and neutrophil count ≤ 1 000 cells/mm^3) should be urgently treated in the hospital with broad spectrum intravenous antibiotics.

IRINOTECAN FKSA administration should be delayed until the neutrophil count is ≥1 500 cells/mm^3.

In patients who experienced severe asymptomatic neutropenia (< 500 cells/mm^3), fever or infections associated with neutropenia, the dose of **IRINOTECAN FKSA** should be reduced. In patients who experienced severe haematologic events, a dose reduction is recommended for subsequent administration (see section 4.2). There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea.

In patients with severe diarrhoea, complete blood cell counts should be performed. Significant correlations were observed between haematological toxicity (decrease in white blood cells and neutrophils at nadir) or diarrhoea intensity and both irinotecan and metabolite SN-38 AUC values in monotherapy.

Liver impairment

Liver function tests should be performed at baseline and before each cycle.

Patients with impaired liver function (bilirubin > 1,0 and ≤ 1,5 times the upper limit of the normal range (ULN) and transaminases 5 times ULN) are at greater risk of developing severe neutropenia or febrile neutropenia and should be closely monitored, including complete blood counts.

Weekly monitoring of complete blood counts should be conducted in patients with bilirubin ranging from 1,5 to 3 times the ULN, due to decrease of the clearance of irinotecan (see section 5.2) and thus increasing the risk of hematotoxicity in this population.

IRINOTECAN FKSA should not be used in patients with a bilirubin > 1,5 times the ULN and the patients with bilirubin > ULN should be followed with caution.

In patients with a bilirubin of < 1,5 times ULN a dose of 350 mg/m^2 is recommended once every 3 weeks (see section 4.2).

Patients with reduced UGT1A1 activity

Patients that are UGT1A1 poor metabolisers, such as patients with Gilbert's syndrome (e.g. homozygous for UGT1A1*28 or *6 variants) are at increased risk for severe neutropenia and diarrhoea following irinotecan treatment. This risk increases with the irinotecan dose level.

Although a precise dose reduction in starting dose has not been established, a reduced irinotecan starting dose should be considered for patients that are UGT1A1 poor metabolisers, especially patients who are administered doses >180 mg/m² or frail patients. Consideration should be given to applicable clinical

guidelines for dose recommendations in this patient population. Subsequent doses may be increased based on individual patient tolerance to treatment.

UGT1A1 genotyping can be used to identify patients at increased risk of severe neutropenia and diarrhoea, however the clinical utility of pre-treatment genotyping is uncertain, since UGT1A1 polymorphism does not account for all the toxicity seen from irinotecan therapy (see section 5.2).

Nausea and vomiting

Prophylactic treatment with an anti-emetic is recommended before each treatment with **IRINOTECAN FKSA**. Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhoea should be hospitalised as soon as possible for treatment.

Acute cholinergic syndrome

If an acute cholinergic syndrome appears (defined as early diarrhoea and a group of symptoms such as sweating, abdominal cramping, lachrymation, miosis and salivation), atropine sulphate (0,25 mg subcutaneously) should be administered unless clinically contraindicated (see section 4.8).

These symptoms may be observed during or shortly after infusion of irinotecan, are thought to be related to the anticholinesterase activity of the irinotecan parent compound, and are expected to occur more frequently with higher irinotecan doses. These symptoms may disappear after atropine administration. Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of **IRINOTECAN FKSA**.

Immunosuppressant effects/increased susceptibility to infections:

Administration of live or live-attenuated vaccines in patients immunocompromised by **IRINOTECAN FKSA**., may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving **IRINOTECAN FKSA**. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Respiratory disorders

Interstitial lung disease presenting as lung infiltration is uncommon during irinotecan therapy. Interstitial lung disease can be fatal. Risk factors possibly associated with the development of interstitial lung disease include the use of pneumotoxic medicine, radiation therapy and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during irinotecan therapy.

Extravasation

While irinotecan is not a known vesicant, care should be taken to avoid extravasation and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site and application of ice is recommended.

Elderly

Due to the greater frequency of decreased hepatic, renal or cardiac function in an elderly patient, dose selection with **IRINOTECAN FKSA** should be cautious in this population

Chronic inflammatory bowel disease and/or bowel obstruction

Patients must not be treated with **IRINOTECAN FKSA** until resolution of the bowel obstruction (see section 4.3).

Renal function

Increases in serum creatinine or blood urea nitrogen have been observed. There have been cases of acute renal failure. These events have generally been attributed to complications of infection or to dehydration related to nausea, vomitting, or diarrhoea. Rare instances of renal dysfunction due to tumour lysis syndrome have also been reported.

Irradiation therapy

Patients who have previously received pelvic/abdominal irradiation are at increased risk of myelosuppression following the administration of irinotecan. Physicians should use caution in treating patients with extensive prior irradiation (e.g. > 25 % of bone marrow irradiated and within 6 weeks prior to start of treatment with irinotecan). Dosing adjustment may apply to this population (see section 4.2).

Cardiac disorders

Myocardial ischaemic events have been observed following irinotecan therapy predominately in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy (see section 4.8).

Consequently, patients with known risk factors should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Vascular disorders

Irinotecan has been rarely associated with thromboembolic events (pulmonary embolism, venous thrombosis, andarterial thromboembolism) in patients presenting with multiple risk factors in addition to the underlying neoplasm.

Others

Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin) of CYP3A4 may alter the metabolism of irinotecan and should be avoided (see section 4.5).

Contraception in women of childbearing potential/men:

Due to the potential for genotoxicity, advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of irinotecan. Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of irinotecan (see section 4.6).

Breast-feeding

Due to the potential for adverse reactions in nursing infants, breast-feeding should be discontinued for the duration of irinotecan therapy (see sections 4.3 and 4.6).

Sorbitol: IRINOTECAN FKSA contains sorbitol. Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

Babies and young children (below 2 years of age) may not yet be diagnosed with HFI. Medicines (containing fructose) given intravenously may have life-threatening effects in individuals with HFI and should not be administered in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicine.

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'

4.5 Interaction with other medicines and other forms of interaction

Concomitant use contraindicated (see section 4.3)

Yellow fever vaccine: Risk of fatal generalised reaction to vaccines.

Saint John's Wort: When St. John's Wort (Hypericum perforatum) is co-administered with Irinotecan there may be a decrease in the active metabolite of irinotecan, SN-38, plasma levels. As a result, St. John's Wort should not be administered with irinotecan.

Live attenuated vaccines: Risk of generalised reaction to vaccines, possibly fatal. Concomitant use is contraindicated during treatment with irinotecan and for 6 months following discontinuation of chemotherapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Concomitant use not recommended (see section 4.4)

Concurrent administration of irinotecan with a strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan of should be avoided (see section 4.4):

Strong CYP3A4 and/or UGT1A1 inducing medicines:

IRINOTECAN FKSA is partly metabolised by cytochrome P450 CYP3A isoenzymes. Inducers of this system e.g. rifampicin, carbamazepine, phenobarbital or phenytoin, reduce exposure to irinotecan and its active metabolite SN-38.

Risk of reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. Several studies have shown that concomitant administration of CYP3A4-inducing anticonvulsant medicines leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant medicines were reflected by a decrease in AUC of SN-38 and SN-38G by 50 % or more. In addition to induction of CYP3A4 enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites. Consideration should be given to starting or substituting non-enzyme inducing anticonvulsants at least one week prior to initiation of IRITERO therapy in patients requiring anticonvulsant treatment. Additionally, with phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicines.

Strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, protease inhibitors, clarithromycin, erythromycin, telithromycin): A study has shown that the co-administration of ketoconazole resulted in a decrease in the AUC of APC of 87 % and in an increase in the AUC of SN 38 of 109 % in comparison to irinotecan given alone.

UGT1A1 inhibitors: (e.g. atazanavir, ketoconazole, regorafenib)

Risk to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration if the combination is unavoidable.

Other CYP3A4 inhibitors: (e.g. crizotinib, idelalisib)

Risk of increase in irinotecan toxicity, due to a decrease in irinotecan metabolism by crizotinib, idelalisib.

Caution for use

Vitamin K antagonists: The use of anticoagulants is common due to increased risk of haemorrhage and thrombotic events in tumoural diseases. If vitamin K antagonist anticoagulants are indicated, an increased frequency of monitoring International Nationalised Ratio (INR) is required due to their narrow therapeutic index, the high intra-individual variability of blood thrombogenicity and the possibility of interaction between oral anticoagulants and anticancer chemotherapy.

Concomitant use to take into consideration

Immunodepressant medicines: (e.g. ciclosporine, tacrolimus): Excessive immunosuppression with risk of lymphoproliferation.

Neuromuscular blocking medicines: Interaction between **IRINOTECAN FKSA** and neuromuscular blocking medicines cannot be ruled out. Medicines with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising medicines may be antagonised. Excess acetylcholine may impair the muscle relaxant action of the non-depolarising medicines and may impair the return of normal muscle tone at the end of anaesthesia. Loperamide should not be given prophylactically.

Other combinations

5-fluorouracil/folinic acid: Coadministration of 5-fluorouracil/ folinic acid in the combination regimen does not change the pharmacokinetic parameters of **IRINOTECAN FKSA.** The pharmacokinetic parameters of **IRINOTECAN FKSA** are comparable to those observed in monotherapy.

Bevacizumab: In one study, irinotecan plasma concentrations were similar in patients receiving irinotecan alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of irinotecan, were analysed in a subset of patients. Concentrations of SN-38 were on average 33 % higher in patients receiving irinotecan in combination with bevacizumab compared with irinotecan alone. Due to high inter-patient variability and limited sampling, it is uncertain if the increase in SN-38 levels observed was due to bevacizumab. There was a small increase in diarrhoea and leukopenia adverse events. More dose reductions of irinotecan were reported for patients receiving irinotecan in combination with bevacizumab.

Cetuximab: There is no evidence that the safety profile of irinotecan is influenced by cetuximab or vice versa.

Antineoplastic medicines: The adverse effects of **IRINOTECAN FKSA**, such as myelosuppression and diarrhoea, is expected to be exacerbated by other antineoplastic medicines having a similar adverse-effect

profile.

Dexamethasone: Lymphocytopenia has been reported in patients receiving. **IRINOTECAN FKSA**, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of lymphocytopenia. Hyperglycaemia has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of **IRINOTECAN FKSA**. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycaemia in some patients.

Laxatives: Laxative use during therapy with **IRINOTECAN FKSA** is expected to worsen the incidence or severity of diarrhoea.

Diuretics: Dehydration secondary to vomiting and/or diarrhoea may be induced by **IRINOTECAN FKSA**. The medical practitioner may wish to withhold diuretics during dosing with **IRINOTECAN FKSA** and during periods of active vomiting or diarrhoea.

Azole antifungals*:* **IRINOTECAN FKSA** clearance is greatly reduced in patients receiving concomitant azole antifungals, leading to increased exposure to the active metabolite, SN-38. Azole antifungals should be discontinued at least 1 week prior to starting **IRINOTECAN FKSA** therapy and should not be administered during **IRINOTECAN FKSA** therapy (see section 4.3).

4.6 Fertility, pregnancy and lactation

Contraception

Due to the potential for genotoxicity, advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of irinotecan (see section 4.4).

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of irinotecan (see section 4.4).

Pregnancy

IRINOTECAN FKSA is contraindicated in pregnancy. There are limited data from the use of irinotecan in pregnant women. Irinotecan has been shown to be embryotoxic and teratogenic in animals (see section 5.3). Therefore, based on results from animal studies and the mechanism of action of irinotecan, **IRINOTECAN FKSA** should not be used during pregnancy.

Women of childbearing potential should not be started on irinotecan until pregnancy is excluded. Pregnancy should be avoided if either partner is receiving irinotecan.

Breastfeeding

IRINOTECAN FKSA is contraindicated in lactation.

The available data are limited but suggested that irinotecan and its metabolite are excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast-feeding should be discontinued for the duration of **IRINOTECAN FKSA** therapy (see sections 4.3 and 4.4).

Fertility

There are no human data on the effect of irinotecan on fertility. In animals adverse effects of irinotecan on the fertility of offspring has been documented (see section 5.3). Prior to starting to take **IRINOTECAN FKSA** consider advising patients on the preservation of gametes.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of **IRINOTECAN FKSA**, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

a. Summary of the safety profile

Dose-limiting adverse reactions of **IRINOTECAN FKSA** are delayed diarrhoea (occurring more than 24 hours after administration) and blood disorders including neutropenia, anaemia and thrombocytopenia. Neutropenia is a dose-limiting toxic effect. Neutropenia is reversible and not cumulative. Severe transient acute cholinergic syndrome may be observed.

The main symptoms are defined as early diarrhoea and various other symptoms such as abdominal pain, sweating, myosis and increased salivation occurring during or within the first 24 hours after the infusion of **IRINOTECAN FKSA.** These symptoms disappear after atropine administration (see section 4.4).

b. **Tabulated list of adverse reactions**

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Neutropenic infection
	Frequency	Pseudomembranous colitis, Sepsis, Fungal infections*, Viral

	unknown	infections†
Blood and lymphatic system disorders	Frequent	Leukopenia, neutropenia, anaemia, thrombocytopenia. febrile neutropenia
	Frequency unknown	Peripheral thrombocytopenia with antiplatelet antibodies
Immune system disorders	Less frequent	Hypersensitivity
	Frequency unknown	Anaphylactic, anaphylactoid reactions.
Endocrine disorders	Less frequent	Diaphoresis, increased salvation
Metabolism and nutrition disorders	Frequent	Decreased appetite
	Less frequent	Hypokalaemia, hypomagnesaemia
	Frequency unknown	Dehydration (due to diarrhoea and vomiting), Hypovolaemia
Nervous system disorders	Frequent	Cholinergic syndrome
	Less frequent	Paraesthesia, abnormal gait, confusion, headache, dizziness.
	Frequency unknown	Transient speech disorders, Muscular contractions involuntary
Eye disorders	Less frequent	Increased lacrimation, myosis
	Frequency unknown	Conjunctivitis, visual disturbance
Cardiac Disorders	Less frequent	Myocardial ischaemia, syncope, bradycardia
	Frequency unknown	Hypertension (during or after infusion), Cardio circulatory failure
Vascular disorders	Frequent	Hypotension or cardiac-circulatory failure Venous and arterial thromboembolic events which includes (angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep vein thrombophlebitis, heart arrest, myocardial infarct, myocardial ischaemia, peripheral

		vascular disorder, pulmonary embolus, sudden death thrombophlebitis, thrombosis, vascular disorder)
	Less frequent	Hypertension (during or after infusion), flushing
	Frequency unknown	Vasodilation
Respiratory, thoracic and mediastinal disorder	Frequent	Dyspnoea (see section 4.4)
	Less frequent	Interstitial lung disease with pulmonary infiltrates, Rhinitis, Upper respiratory tract infection, interstitial pneumonia (see section 4.4)
	Frequency unknown	Hiccups
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, vomiting, dehydration, (associated with diarrhoea and /or vomiting) constipation, abdominal pain and mucositis, anorexia, stomatitis.
	Less frequent	Rectal disorder, gi monilia, intestinal obstruction, ileus or gastrointestinal haemorrhage, intestinal perforation, transient increase in amylase and lipase, anorexia, mucositis, abdominal enlargement, bloated feeling or gas, Clostridium difficile induced pseudo-membranous colitis, indigestion
	Frequency unknown	Intestinal perforation, intestinal obstruction, gastrointestinal haemorrhage, toxic megacolon, asymptomatic pancreatitis, Ileus, Colitis, Typhlitis, Colitis ischaemic, Colitis ulcerative
Hepatobiliary disorders	Frequent	Hyperbilirubinemia
	Frequency unknown	Steatohepatitis, Hepatic steatosis
Skin and subcutaneous tissue disorders	Frequent	Alopecia (reversible), cutaneous reactions such as dry skin, pruritus, skin discolouration
	Less frequent	Rash
	Frequency	Skin reaction, sweating

	unknown	
Musculoskeletal and connective tissue disorders	Frequent	Muscular contraction, or cramps
Renal and urinary disorders	Less frequent	Urinary tract infection
	Frequency unknown	Renal insufficiency, Renal impairment and acute renal failure
Reproductive system and breast disorders	Less frequent	Breast pain
General disorders and administration site conditions	Frequent	Reaction at infusion site, fever, acute cholinergic syndrome (symptoms include early diarrhoea, abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilation, sweating, chills, malaise, dizziness, visual disturbances, miosis, lacrimation and increased salivation), mucosal inflammation, asthenia, pyrexia, extravasation, tumour lysis syndrome
	Frequency unknown	Infusion site reaction, transient speech disorders
Investigations	Frequent	Transient increases in serum levels of transaminases (ALT/AST), alkaline phosphatase, bilirubin, creatinine
	Frequency unknown	Increases in amylase and lipase; hypokalaemia, hyponatraemia (associated with diarrhoea and vomiting) and transaminases, increased GGTP (gamma-glutamyl transpeptidase)

*e.g. Pneumocystis jirovecii pneumonia, bronchopulmonary aspergillosis, systemic candida.

†e.g. Herpes zoster, influenza, hepatitis B reactivation, cytomegalovirus colitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any

suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) "**Adverse Drug Reactions and Product Quality Reporting Form**", found on SAHPRA website https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdose

Overdosage may occur at dosages twice the recommended dosage, and can be fatal.

The most significant adverse reactions reported were severe neutropenia and diarrhoea.

Treatment of overdose

There is no antidote for **IRINOTECAN FKSA** and the only possible treatment is maximum supportive treatment to prevent dehydration due to diarrhoea and to treat infectious complications.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A 26 Cytostatic agents

Pharmacotherapeutic group: Cytostatic topoisomerase I inhibitor.

ATC Code: L01CE02

Irinotecan is a semi-synthetic derivative of camptothecin. It is an antineoplastic medicine, which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN- 38, which was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines.

The inhibition of DNA topoisomerase I by irinotecan or SN-38, induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found to be time dependent and was specific to the S phase.

In vitro, irinotecan and SN-38 were found not to be significantly recognised by the P-glycoprotein, and displays cytotoxic activities against doxorubicin and vinblastine resistant cell lines.

Furthermore, irinotecan has a broad antitumour activity *in vivo* against murine tumour models (P03 pancreatic ductal adenocarcinoma, MA16/C mammary adenocarcinoma, C38 and C51 colon adenocarcinoma) and against human xenografts (Co-4 colon. adenocarcinoma, Mx-1 mammary adenocarcinoma, ST-15 and SC-16 gastric adenocarcinomas). Irinotecan is also active against tumours

expressing the P-glycoproteinMDR (vincristine- and doxorubicin-resistant P388 leukaemias).
Beside the antitumour activity of irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

5.2 Pharmacokinetic properties

In a phase I study, in 60 patients with a dosage regimen of a 30-minute intravenous infusion of 100 to 750 mg/m^2 every three weeks, irinotecan showed a biphasic or three-phasic elimination profile. The mean plasma clearance was 15 L/h/m^2 and the volume of distribution at steady state (Vss) quite large: 157 L/m^2. The mean plasma half-life of the first phase of the triphasic model was 12 minutes, of the second phase 2,5 hours and the terminal phase half-life was 14,2 hours. SN-38 showed a biphasic elimination profile with a mean terminal elimination half-life of 13,8 hours. At the recommended dose of 350 mg/m^2, the mean irinotecan and SN-38 peak plasma concentrations were 7,7 µg/ml and 56 ng/ml, respectively and were reached at the end of the infusion. The mean area under the curve (AUC) values were 34 µg.h/ml and 451 ng.h/ml, respectively. A large inter-individual variability in pharmacokinetic parameters is generally observed for SN-38.
In vitro, the plasma protein binding for irinotecan and SN-38 were approximately 65 % and 95 % respectively.
Mass balance and metabolism studies with 14C-labelled irinotecan have shown that more than 50 % of an intravenously administered dose of irinotecan is excreted unchanged, with 33 % in the faeces via the bile and 22 % in urine.
Two metabolic pathways, each representing at least 12 % of the dose, have been identified: oxidative metabolism at the terminal piperidine ring by cytochrome P450 3A enzymes which results in an aminopentanoic acid derivative (APC) and a primary amine derivate and hydrolysis by carboxylesterases into the active metabolite SN-38.
SN-38 is mainly eliminated by glucuronidation and further by biliary and renal excretion (less than 0,5 % of the irinotecan dose). Unchanged irinotecan is the major entity in plasma followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity and no other circulating metabolites have been detected. Irinotecan clearance is decreased by about 40 % in patients with bilirubinaemia between 1,5 and 3 times the upper normal limit. In these patients a 200 mg/m^2 irinotecan dose leads to plasma exposure comparable to that observed at 350 mg/m^2 in cancer patients with normal liver

parameters.

Co-administration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Sorbitol,

lactic acid,

sodium hydroxide, (for pH-adjustment)

water for injection.

6.2 Incompatibilities

This medicine must not be mixed with other medicines.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Protect from light.

For intravenous use.

Single use only.

6.5 Nature and contents of container

IRINOTECAN 40 mg/2 ml FKSA is packed into a 6 ml Type-I, amber, glass vial with a grey chlorobutyl

rubber stopper and a 20 mm Aluminium flip-off over seal of green colour. 1 x 40 mg/2 ml vial packed into an outer cardboard carton.

IRINOTECAN 100 mg/5 ml FKSA is packed into a 6 ml Type-I, amber, glass vial with a grey chlorobutyl rubber stopper and a 20 mm Aluminium flip-off over seal of blue colour. 1 x 100 mg/5 ml vial packed into an outer cardboard carton.

IRINOTECAN 300 mg/15 ml FKSA is packed into a 20 ml Type-I, amber, glass vial with a grey chlorobutyl rubber stopper and a 20 mm Aluminium flip-off over seal of red colour. 1 x 300 mg/15 ml vial packed into an outer cardboard carton.

IRINOTECAN 500 mg/25 ml FKSA is packed into a 30 ml, Type-I, amber, glass vial with a grey chlorobutyl rubber stopper and a 20 mm Aluminium flip-off over seal of yellow colour. 1 x 500 mg/25 ml vial packed into an outer cardboard carton.

6.6 Special precautions for disposal and other handling

Special handling precautions for cytostatic medicines should be followed:

Only trained personnel should reconstitute the medicine in a designated area.

IRINOTECAN FKSA is an antineoplastic medicine and, caution should be exercised when handling it and preparing **IRINOTECAN FKSA** solutions.

The work surface should be covered with disposable plastic-backed absorbent paper. Adequate protective gloves and clothing should be worn.

If **IRINOTECAN FKSA** solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If **IRINOTECAN FKSA** solution or infusion solution should come into contact with the eyes or mucous membranes, wash immediately and thoroughly with water. The cytotoxic preparation must not be handled by pregnant staff. Adequate care and precautions should be taken in the disposal of items used to reconstitute the medicine.

Preparation for the intravenous infusion administration

Aseptically withdraw the required amount of **IRINOTECAN FKSA** solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 0,9 % sodium chloride solution or 5 % dextrose solution. The infusion should then be thoroughly mixed by manual rotation. **IRINOTECAN FKSA** infusion solution should be infused into a peripheral or central vein. **IRINOTECAN FKSA** should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90

minutes.

If any precipitate is observed in the vials before or after reconstitution, the product should be discarded according to standard procedures for cytotoxic medicines. Do not admix with other medications.

For single use only. Any unused portion should be discarded.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd.

Stand 7, Growthpoint Park, Business Park

162 Tonetti Street

Halfway House, Extension 7

Midrand, 1685

South Africa

8 REGISTRATION NUMBER(S)

IRINOTECAN 40 mg/2 ml FKSA: 45/26/0915

IRINOTECAN 100 mg/5 ml FKSA: 45/26/0916

IRINOTECAN 300 mg/15 ml FKSA: 45/26/0917

IRINOTECAN 500 mg/25 ml FKSA: 45/26/0918

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 26 November 2015

10 DATE OF REVISION OF THE TEXT

06 November 2024